Common Issues in Clinical Trials: Patient Recruitment, Retention, Eligibility and Screening Failure

Moderators
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Rebecca Taub, Madrigal Pharmaceuticals

Presenter
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Common Issues in Clinical Trials: Patient Recruitment, Retention, Eligibility and Screening Failure

Sven Francque, MD, PhD

Universiteit Antwerpen

- Recruitment and referral
- Patient recruitment and retention
- Eligibility and screening failure

Recruitment and referrals

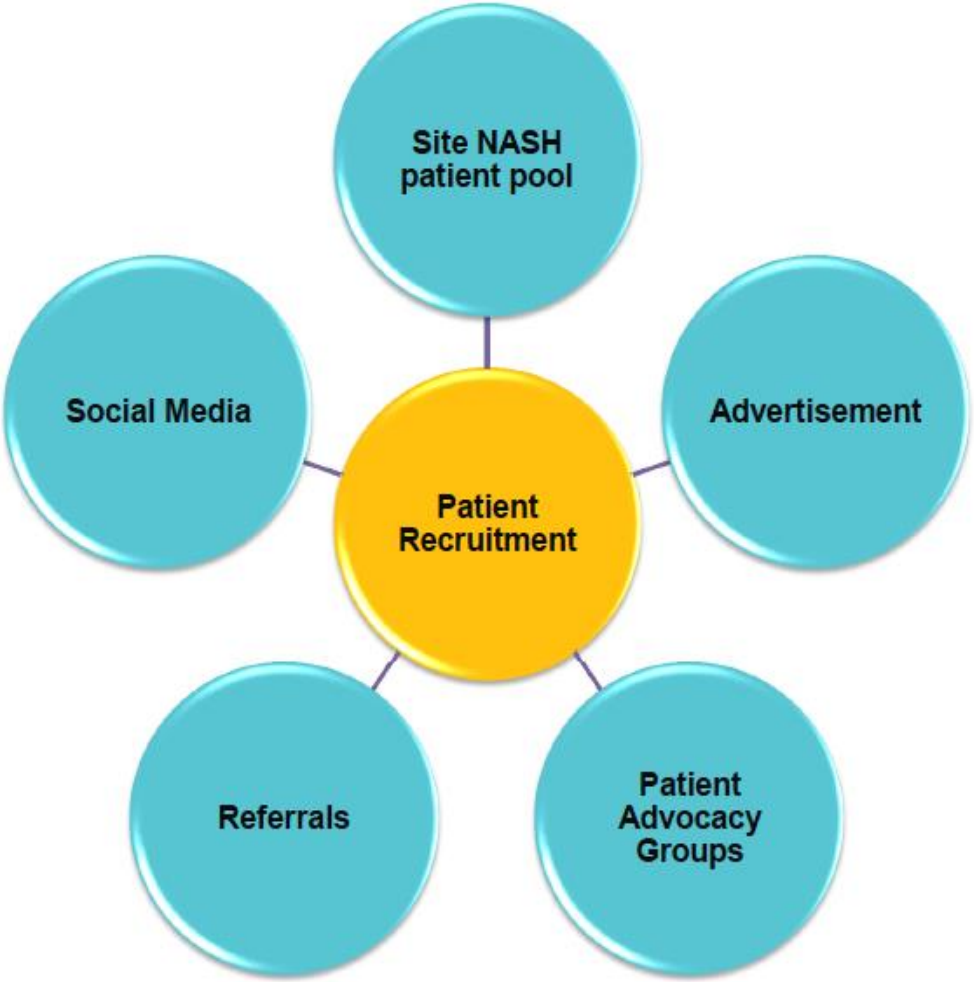
Current status

- Previously:
  - Few trials
  - Phase 2
  - Expert centres
  - “historical” patients

  - Recruitment targets relatively easily reached in rather short time frame in a limited number of large volume centres

Current status

- Previously
- Currently
  - Numerous competing trials
  - Phase 3
  - More or less the same target population


Site NASH patient pool
Social Media
Advertisement
Patient Recruitment
Referrals
Patient Advocacy Groups

- Increase awareness
  - Websites
    - General information
    - Trial-specific website
      - EC approval?
      - Experience?
    - Country-specific regulations and habits
  - Initiatives on general information
    - Media
      - NASH Education Program
    - Social media

R&D
FXR
Therapeutic Focus
PBC
NASH
PSC
Pipeline
Expanded Access
Discovery Compounds
Scientific Presentations

Nonalcoholic steatohepatitis (NASH)

Nonalcoholic steatohepatitis (NASH) is a disease with epidemic proportions

- Overview of NASH
- Natural history of NASH
- Epidemiology of NASH
- Identifying patients with NASH
- Symptoms of NASH
- Potential complications of NASH

The changing landscape of NAFLD and NASH: A global perspective.

Overview of NASH

- Nonalcoholic fatty liver disease (NAFLD) is associated with excessive fat in the liver (steatosis) and can progress to NASH, which is defined by the histologic hallmarks of inflammation, cell death, and fibrosis
- Primary NASH is associated with insulin resistance
- Secondary NASH is rare in adults and is caused by medical or surgical conditions, or drugs such as tamoxifen

Natural history of NASH

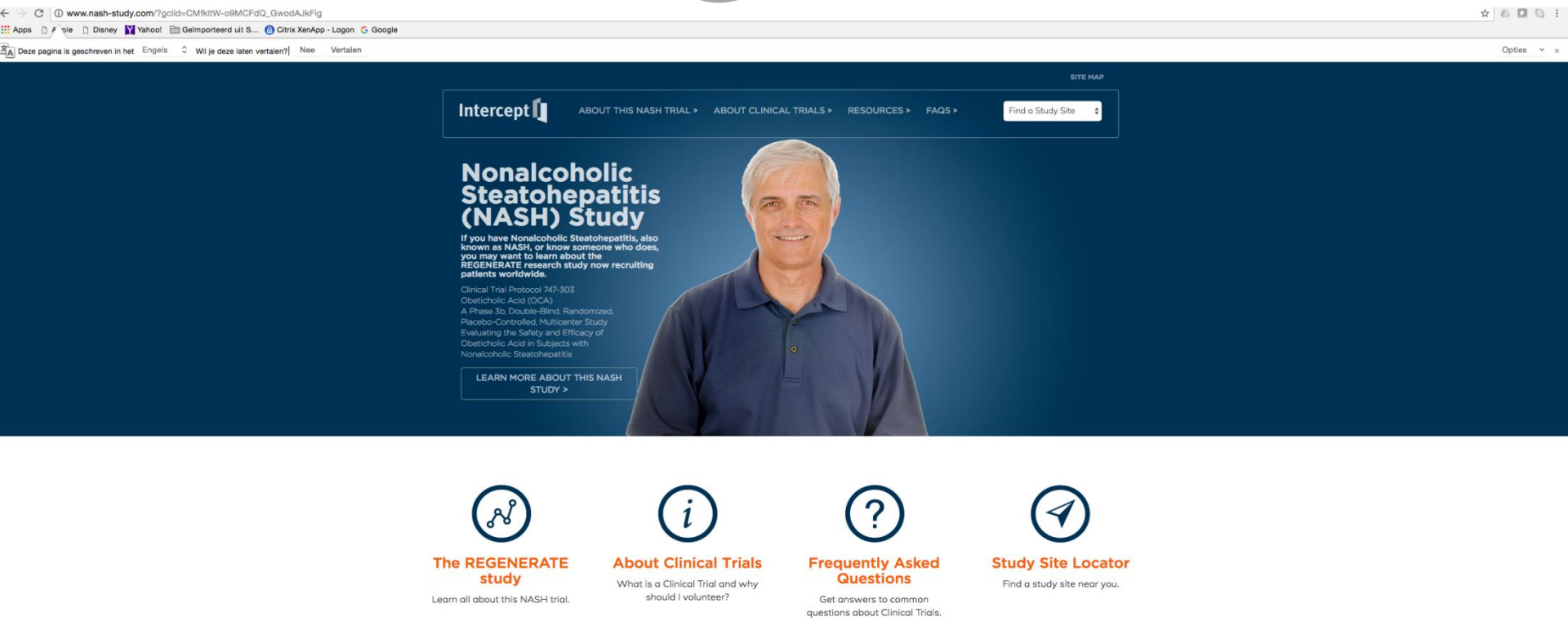
- Histologically, NASH is similar to alcohol-induced steatohepatitis, and is associated with factors that cause an increase in oxidative stress and promote expression of proinflammatory cytokines
- NASH is the most common cause of fibrosis and cirrhosis in patients with unexplained increased alanine aminotransferase

Epidemiology of NASH

- NASH is one of the most common liver diseases
- NASH is the third leading cause of liver transplant in the US
- Since 2001, liver transplants attributed to NASH have increased tenfold
- In the US, more than 12% of the general population has NASH
  - Approximately 2.7% have advanced liver fibrosis due to the disease
- Studies show that 5% to 25% of the growing number of patients with NASH develop cirrhosis within 7 years of follow-up

Identifying patients with NASH

Symptoms of NASH


www.nash-study.com/?gclid=CMfkItW-o9MCFdQ_GwodAJkFig
Apps
Disney
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Citrix XenApp - Logon
Google
Deze pagina is geschreven in het Engels
Wil je deze laten vertalen?
Nee
Vertalen
Opties
SITE MAP
Intercept
ABOUT THIS NASH TRIAL >
ABOUT CLINICAL TRIALS >
RESOURCES >
FAQS >
Find a Study Site
Nonalcoholic Steatohepatitis (NASH) Study
If you have Nonalcoholic Steatohepatitis, also known as NASH, or know someone who does, you may want to learn about the REGENERATE research study now recruiting patients worldwide.
Clinical Trial Protocol 747-303
Obeticholic Acid (OCA)
A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis
LEARN MORE ABOUT THIS NASH STUDY >
The REGENERATE study
Learn all about this NASH trial.
About Clinical Trials
What is a Clinical Trial and why should I volunteer?
Frequently Asked Questions
Get answers to common questions about Clinical Trials.
Study Site Locator
Find a study site near you.

Therapeutic areas
- Metabolic diseases
- Liver diseases
- **Nonalcoholic steatohepatitis (NASH)**
- Cholestatic liver diseases
- Inflammation and autoimmune diseases
- Inflammatory Bowel Disease

Nonalcoholic steatohepatitis (NASH)

"NASH", or nonalcoholic steatohepatitis, is a liver disease characterized by an accumulation of fat (lipid droplets), along with inflammation and degeneration of hepatocytes.
Once installed, the disease is accompanied with a high risk of cirrhosis, a state where the liver functions are altered and can progress to liver insufficiency. Thereafter, the NASH often progresses to liver cancer.

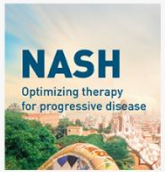
To face this challenge, Genfit focuses on bringing therapeutic solutions to combat the major health concerns of NASH. At Genfit, we are committed to ensuring that our drug candidate Elafibranor (GFT505) becomes a first-in-line medicine in its field, thus bringing a therapeutic solution to patients who currently have no treatment options.

The treatment of NASH is a major therapeutic need

According to the leading hepatologists, NASH is considered a « ticking time bomb » and the regulatory authorities (FDA and EMA) have supported the needs for the discovery of efficient treatments for this disease.
The therapeutic needs are tremendous worldwide as the number of NASH cases is constantly expanding, together with the diabetes and obesity epidemic. Hence, in the United States, the NASH prevalence is estimated over 12% the adult population. For the diabetic population, the number rises up to 22%. It is noteworthy that between 15 to 25% of NASH patients will develop cirrhosis.

There are numerous risk factors and predictors of NASH: age, obesity and BMI (Body Mass Index), insulin sensitivity, dyslipidemia, hypertension and increase of liver enzymes. In turn, patients with NASH have increased risks for myocardial infarction, stroke or peripheral vascular accident.

EASL ILC 2016
GENFIT Symposium



NASH: Optimizing therapy for progressive disease
April 2016

WATCH

Nonalcoholic steatohepatitis

www.genfit.com/therapeutic-areas/nash/

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Deze pagina is geschreven in het Engels. Wil je deze laten vertalen? Nee Vertalen

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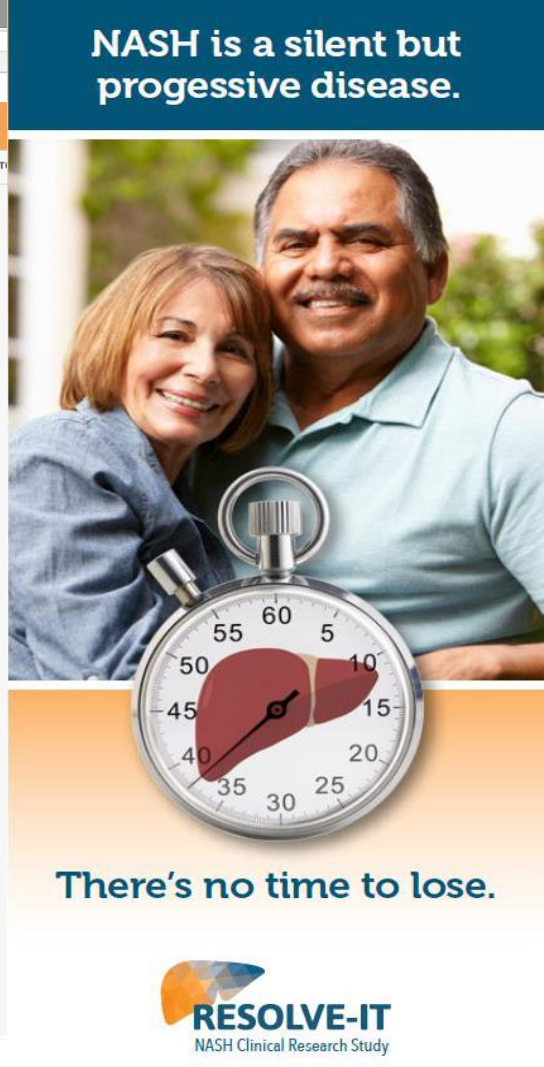

Nieuw tabblad | Allergan Clinical Trials - Allerg | Allergan Clinical Trials - Clinic

www.allerganclinicaltrials.com

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Allergan

Trial Results | Inquiries | Patient Level Data Request | More Info

Welcome

Allergan, Inc. is a multi-specialty health care company focused on discovering, developing and commercializing innovative pharmaceuticals, biologics and medical devices that enable people to live life to its greatest potential - to see more clearly, move more freely, express themselves more fully. We design our clinical trials in a scientific manner to investigate the benefits, risks and value of future or current products.

Trial Inquiries

Allergan-sponsored phase 2,3 and 4 trials are posted on www.clinicaltrials.gov.

Click here for more info about participating in Allergan-sponsored clinical trials.

More Information

We conduct clinical trials in an ethical manner and adhere to ICH guidelines, FDA, EU and other regulations.

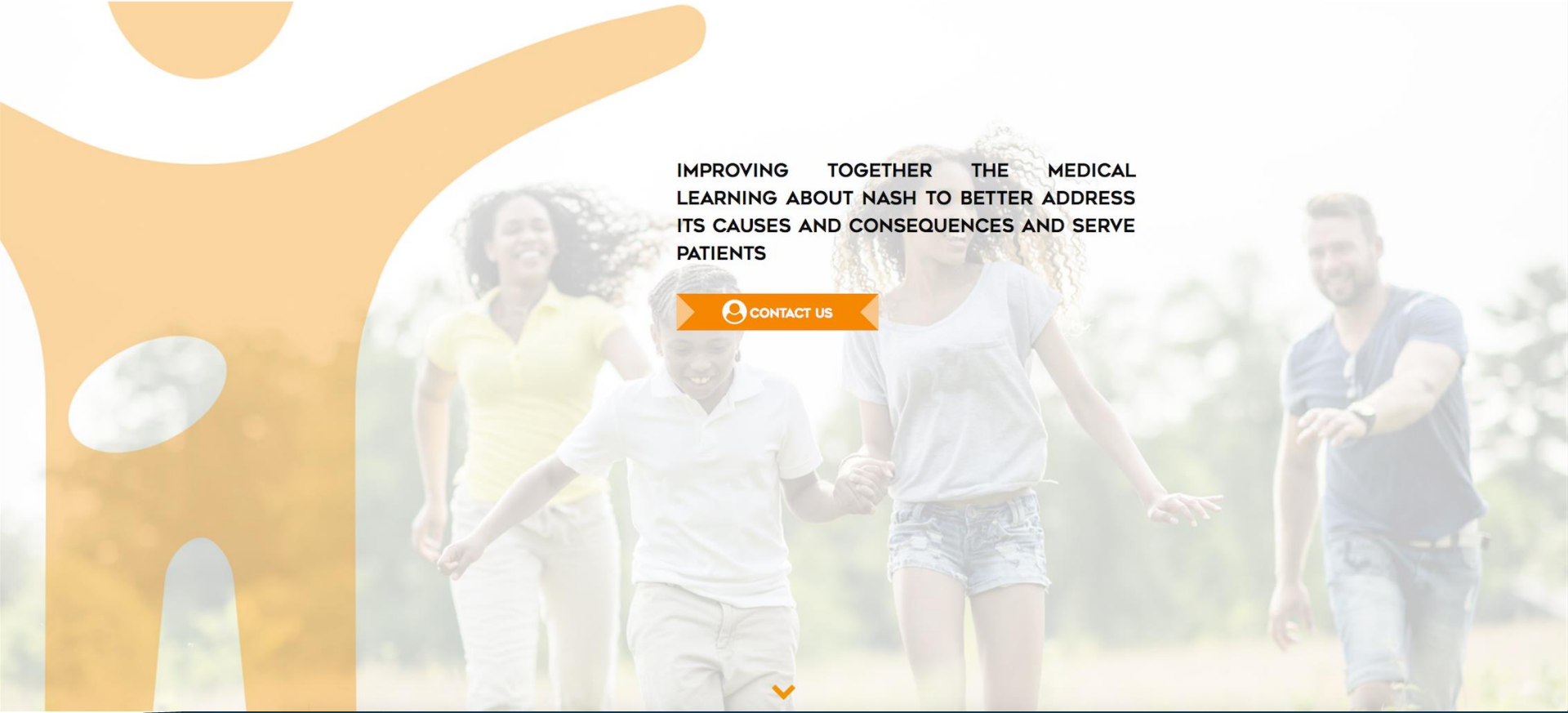
Click here for more info regarding the clinical trial process.

Click here for definitions and more information on Clinical Research Study Phases.

Home | Trial Results | Inquiries | Patient Level Data Request | More Info | Privacy Statement

THE NASH EDUCATION PROGRAM

PRESS RELEASE



IMPROVING TOGETHER THE MEDICAL LEARNING ABOUT NASH TO BETTER ADDRESS ITS CAUSES AND CONSEQUENCES AND SERVE PATIENTS

CONTACT US

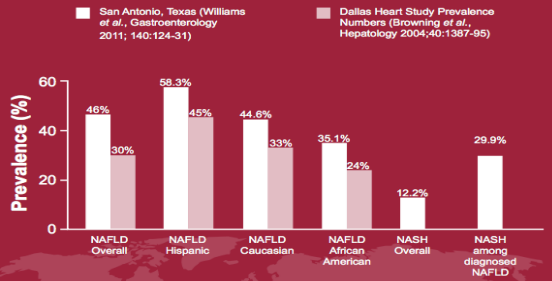
THE NASH EDUCATION PROGRAM
A GENFIT INITIATIVE

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) & NON-ALCOHOLIC STEATOHEPATITIS (NASH)

ADDRESSING A GROWING SILENT EPIDEMIC

PREVALENCE OF NAFLD/NASH

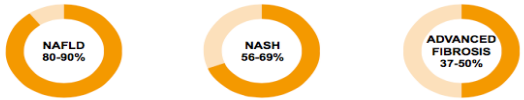
USA Prevalence in Middle Age Patients



Worldwide prevalence of NAFLD: 20-30%

- 13-44% in Middle Eastern countries
- Approx. 20% in Asian countries
- Approx. 30% in European countries
- NASH worldwide prevalence unknown (estimate from U.S. study: 6-8%)

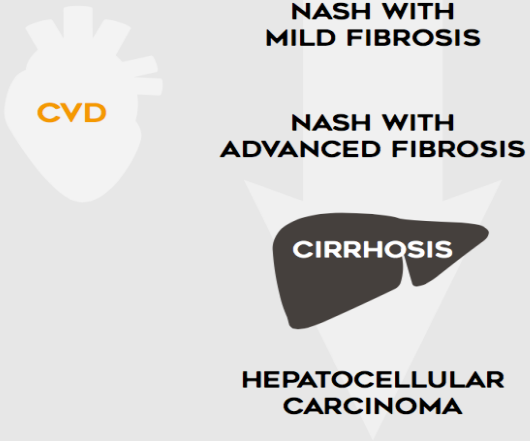
NAFLD/NASH PREVALENCE AMONG PATIENTS WITH DIABETES



NAFLD/NASH PREVALENCE AMONG OBESE PATIENTS

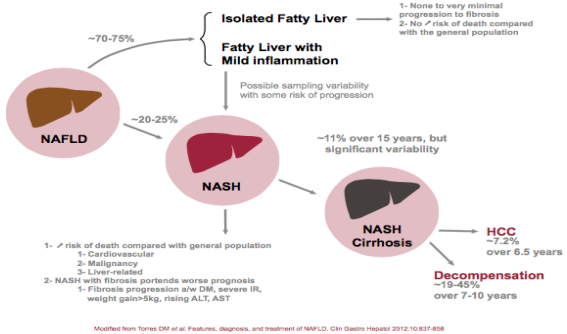
Prevalence among bariatric surgery patients

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)



NAFLD is an umbrella term that encompasses the spectrum of fatty liver disease, from isolated steatosis to cirrhosis and liver cancer with underlying CVD risk.

NATURAL HISTORY OF NAFLD

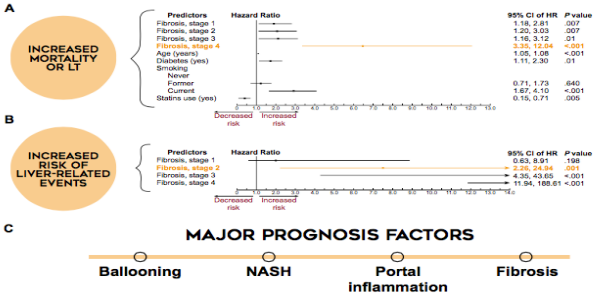


Modified from Torres DM et al. Features, diagnosis, and treatment of NAFLD. Clin Gastro Hepatol 2012;10:837-858

- Progression of isolated steatosis to cirrhosis is very rare
- Fatty liver with inflammation but not NASH may progress but as slower rate than NASH
- NASH with fibrosis is at greater risk for disease progression
- Patients with NASH and metabolic syndrome are also an enriched population for disease progression
- NAFLD/NASH is now the second leading cause for liver transplantation in the U.S.

HIERARCHY OF HISTOLOGIC FEATURES

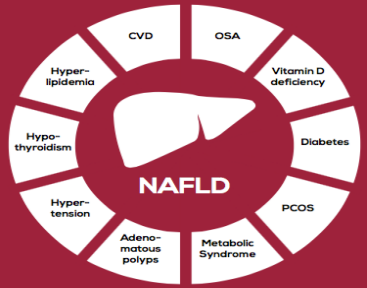
Associated with disease progression and mortality



NAFLD & MORTALITY: TOP 3 CAUSES

1. CARDIOVASCULAR DISEASE (CVD)
2. ALL CAUSE MALIGNANCY
3. LIVER-RELATED DEATH

CONDITIONS ASSOCIATED WITH NAFLD



Modified from Torres DM et al. Features, diagnosis, and treatment of NAFLD. Clin Gastro Hepatol 2012;10:837-858

DIAGNOSIS

- AASLD practice guidelines require liver biopsy to diagnose NASH
- Liver enzymes can be normal in up to 60% of patients with NASH
- No non-invasive test with sufficient sensivity or specificity to rule in or rule out NASH

RED FLAGS INCREASING PROBABILITY FOR NASH

When deciding whom to biopsy

- Age
- Gender
- Hispanic
- Hypertension
- Obesity
- ALT and AST level
- AST/ALT ratio
- Insulin level
- PNPLA3

No lab test or imaging study will be able to predict with 100% accuracy

All variables have been shown to predict NASH

TREATMENT

- Diet, lifestyle modification and exercice remain the top priority. Ultimate goal is to achieve 10% weight loss as this has been shown to improve all histopathologic parameters of NASH.
- Consideration in non-diabetics can be given to vitamin E at doses of 800-1000 IU daily.
- Consideration can also be given to those patients with diabetes to add pioglitazone 30-45 mg daily.

Diet and exercise are not always satisfactory options, and there is a lack of treatment. To address this unmet need, enrollment in one of the clinical trials underway can be considered.

NASH: KEY CONSIDERATIONS

- NASH is the liver manifestation of metabolic diseases. NASH patients are often obese, have type 2 diabetes, and cardiovascular disease.
- NASH is the underlying cause of cirrhosis and its complications: treating NASH is the appropriate approach to prevent progression to cirrhosis.
- Liver biopsy is required to diagnose NASH.
- How to reverse NASH: stop the disease activity i.e. necroinflammation (ballooning + inflammation) that is the driver leading to liver fibrosis and progressive liver fibrosis.
- NASH therapies should be efficacious against both the underlying liver disease and comorbid conditions associated with NAFLD such as insulin resistance, diabetes, and hyperlipidemia.
- Because NASH is a chronic and silent disease, therapies should be safe and well tolerated.

THE NASH EDUCATION PROGRAM
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4. Quels projets concrets pour *The NASH Education Program™* en 2017 ?

2. Video éducative KOLs

De quoi s'agit-il ?

« **NASH, anticipating an impending storm** » : paroles de KOLs permettant d'apporter un éclairage simple et clair sur la NASH

Objectif

Expliquer à une audience internationale (médecins, patients, grand public) quels sont les ressorts de la maladie : causes, risques, conséquences, traitements, etc.

Mise en œuvre

- Interviews de KOLs de renommée mondiale (hépatologie, endocrinologie), et/ou membres actifs du Liver Forum, et/ou membres du comité de pilotage international de l'essai clinique de Phase 3 RESOLVE-IT dans la NASH
- Diffusion web, lors d'évènements scientifiques, etc.

- General practitioners
  - Curriculum
  - Post-graduates, conferences, meetings
  - Information leaflets
  - Information leaflets and posters in waiting room?

- Specialists
  - Different specialties
    - Diabetology
      - Common guidelines
      - Seek for collaboration and implementation of recommendations
        - » Attendance at meetings

- Specialist
  - Obesity clinics, gastroenterologist, cardiologists

  - Postgraduates & conferences & meetings
  - Information leaflets
  - Information leaflets and posters waiting rooms
  - Referral letters
  - Other media?

  - Information letter, newsletters for potential referring physicians
  - Letter to inform general practitioner or referring physician of screening and/or inclusion
  - Call with treating physician?

REFERRAL FORM FOR NASH PATIENTS

Patients Name _____ Date of Birth _____

Contact Phone Number _____ Contact Email _____

Please select the following items that apply to this patient:

- ☐ DM HgbA1c < 9.6
- ☐ Obesity
- ☐ HTN
- ☐ Post-Menopausal
- ☐ Hispanic
- ☐ AST > 40
- ☐ HgbA1c ≥ 5.8
- ☐ > 2-3 drinks per day (males) or > 1-2 drinks current day (females)
- ☐ Positive History of ETOH abuse
- ☐ Imaging showing Hepatic Steatosis
  - ☐ US
  - ☐ CT
  - ☐ MRI

Please answer one or more of the following:

1. Is the NAFLD Fibrosis Score ≥ -1.455 ☐Yes ☐No (http://nafldscore.com/)

   CLICK HERE FOR NFS CALCULATOR

   (http://nafldscore.com/)

2. Is the FIB-4 ≥ 1.3 ☐Yes ☐No

   CLICK HERE FOR FIB-4 CALCULATOR

   (http://www.microsofttranslator.com/BV.aspx?ref=IE8Activity&a=http%3A%2F%2Fwww.hepatitisc.uw.edu%2Fpage%2Fclinical-calculators%2Ffib-4)

3. APRI ≥ 0.5 ☐Yes ☐No

   CLICK HERE FOR APRI CALCULATOR

   (http://www.microsofttranslator.com/bv.aspx?from=&to=en&a=http%3A%2F%2Fwww.hepatitisc.uw.edu%2Fpage%2Fclinical-calculators%2Fapri)

4. Fibroscan > 7 KPA ☐Yes ☐No
5. Has a liver biopsy been performed? ☐Yes ☐No

With your referral please send all relevant information including: relevant medical history, recent consultation, medications, labs, imaging and liver biopsy.

We appreciate your referral.

Referring Provider: _____

Referring Provider phone: _____

Please fax the completed form to: **fax (210-572-5766)**

- Specialist
  - Obesity clinics, gastroenterologist, cardiologists

  - Postgraduates & conferences & meetings
  - Information leaflets
  - Information leaflets and posters waiting rooms
  - Referral letters
  - Other media?

  - Information letter, newsletters for potential referring physicians
  - Letter to inform general practitioner or referring physician of screening and/or inclusion
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Only 24% of academic gastroenterologists and hepatologists in the USA routinely perform liver biopsy[1]

[1]Rinella *et al*, Hepatology 2016

Diabetes Care
THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
January 2017 Volume 40, Supplement 1

Standards of Medical Care in Diabetes—2017

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- Management of Preexisting Type 1 Diabetes and Type 2 Diabetes in Pregnancy
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- Pregnancy and Drug Considerations

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FORUM for Collaborative RESEARCH

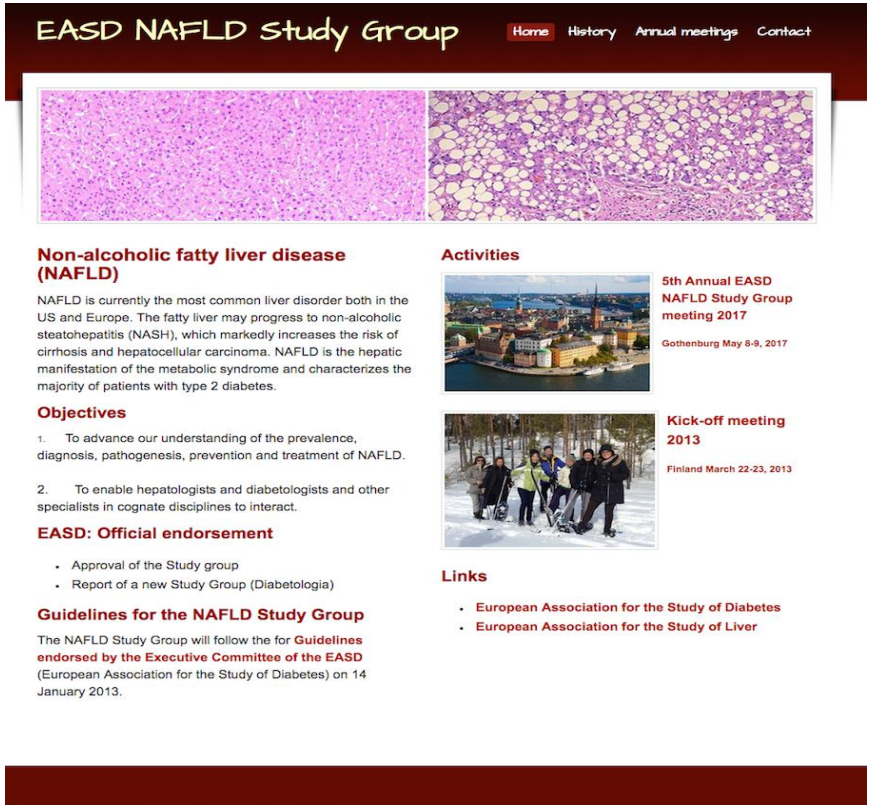
UZA kennis / ervaring / zorg

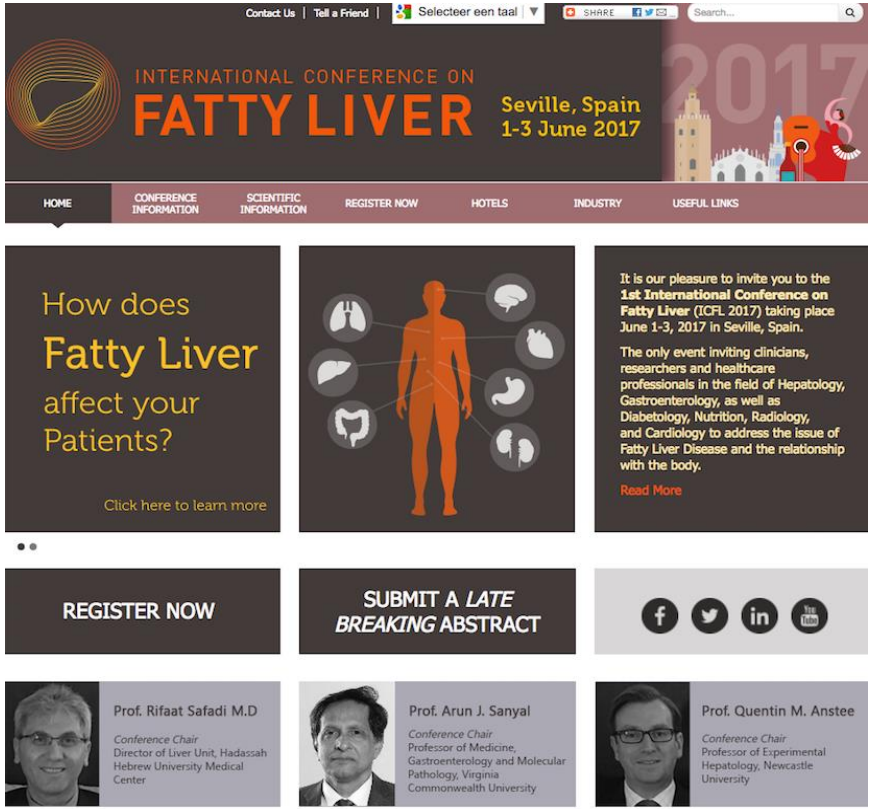
Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)


EASD NAFLD Study Group
Home
History
Annual meetings
Contact
Non-alcoholic fatty liver disease (NAFLD)
NAFLD is currently the most common liver disorder both in the US and Europe. The fatty liver may progress to non-alcoholic steatohepatitis (NASH), which markedly increases the risk of cirrhosis and hepatocellular carcinoma. NAFLD is the hepatic manifestation of the metabolic syndrome and characterizes the majority of patients with type 2 diabetes.
Objectives
1. To advance our understanding of the prevalence, diagnosis, pathogenesis, prevention and treatment of NAFLD.
2. To enable hepatologists and diabetologists and other specialists in cognate disciplines to interact.
EASD: Official endorsement
Approval of the Study group
Report of a new Study Group (Diabetologia)
Guidelines for the NAFLD Study Group
The NAFLD Study Group will follow the for Guidelines endorsed by the Executive Committee of the EASD (European Association for the Study of Diabetes) on 14 January 2013.
Activities
5th Annual EASD NAFLD Study Group meeting 2017
Gothenburg May 8-9, 2017
Kick-off meeting 2013
Finland March 22-23, 2013
Links
European Association for the Study of Diabetes
European Association for the Study of Liver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INTERNATIONAL CONFERENCE ON
FATTY LIVER
Seville, Spain
1-3 June 2017
2017
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CONFERENCE INFORMATION
SCIENTIFIC INFORMATION
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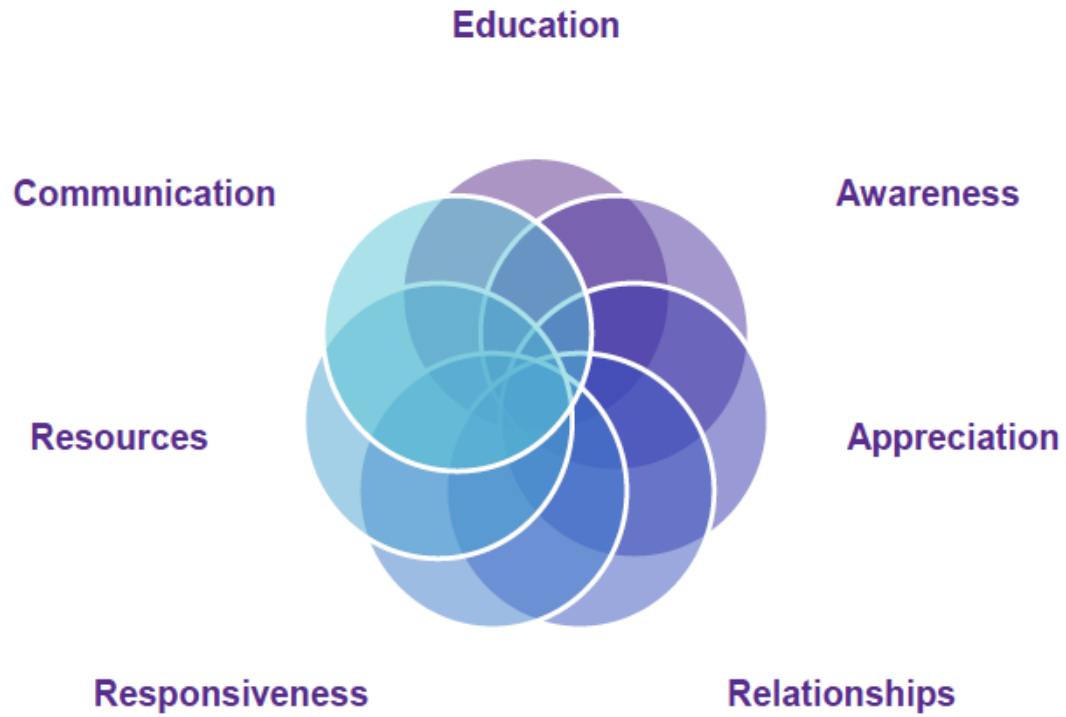
INDUSTRY
USEFUL LINKS
How does Fatty Liver affect your Patients?
Click here to learn more
It is our pleasure to invite you to the 1st International Conference on Fatty Liver (ICFL 2017) taking place June 1-3, 2017 in Seville, Spain.
The only event inviting clinicians, researchers and healthcare professionals in the field of Hepatology, Gastroenterology, as well as Diabetology, Nutrition, Radiology, and Cardiology to address the issue of Fatty Liver Disease and the relationship with the body.
Read More
REGISTER NOW
SUBMIT A LATE BREAKING ABSTRACT
Prof. Rifaat Safadi M.D
Conference Chair
Director of Liver Unit, Hadassah Hebrew University Medical Center
Prof. Arun J. Sanyal
Conference Chair
Professor of Medicine, Gastroenterology and Molecular Pathology, Virginia Commonwealth University
Prof. Quentin M. Anstee
Conference Chair
Professor of Experimental Hepatology, Newcastle University

Patient recruitment and retention

- Recruitment tools
  - Increase general awareness
    - Trial-specific information?
    - Websites, flyers,…
  - Role of general practitioners and referring physicians
    - Communication!
    - Template letters
    - Calls

- Difficulties in motivating the patients to participate
  - Lack of knowledge
    - Good information = time consuming
  - Biopsy (need? Complications? Alternatives?)
    - Good information, experienced physician to perform biopsy
  - Placebo
    - No approved therapy
  - Long term study
    - Information
  - Biopsy result itself can help!
  - Letter to inform general practitioner or referring physician of eligibility
  - Call with treating physician?


Education
Communication
Awareness
Resources
Appreciation
Responsiveness
Relationships

Patient retention

- Long term trials
- Potential side effects
  - Communication and complete information
  - Realistic expectations

- Follow-up biopsies
  - Experienced physician

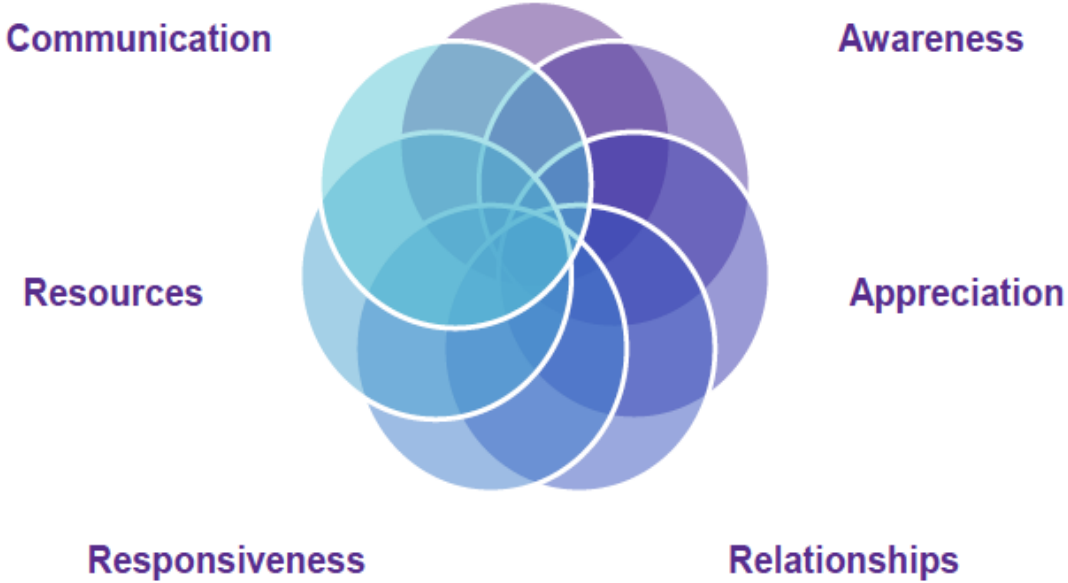
- Calls
- Apps (mPAL Trial Guide App)
- Websites
- Trial booklets
- …

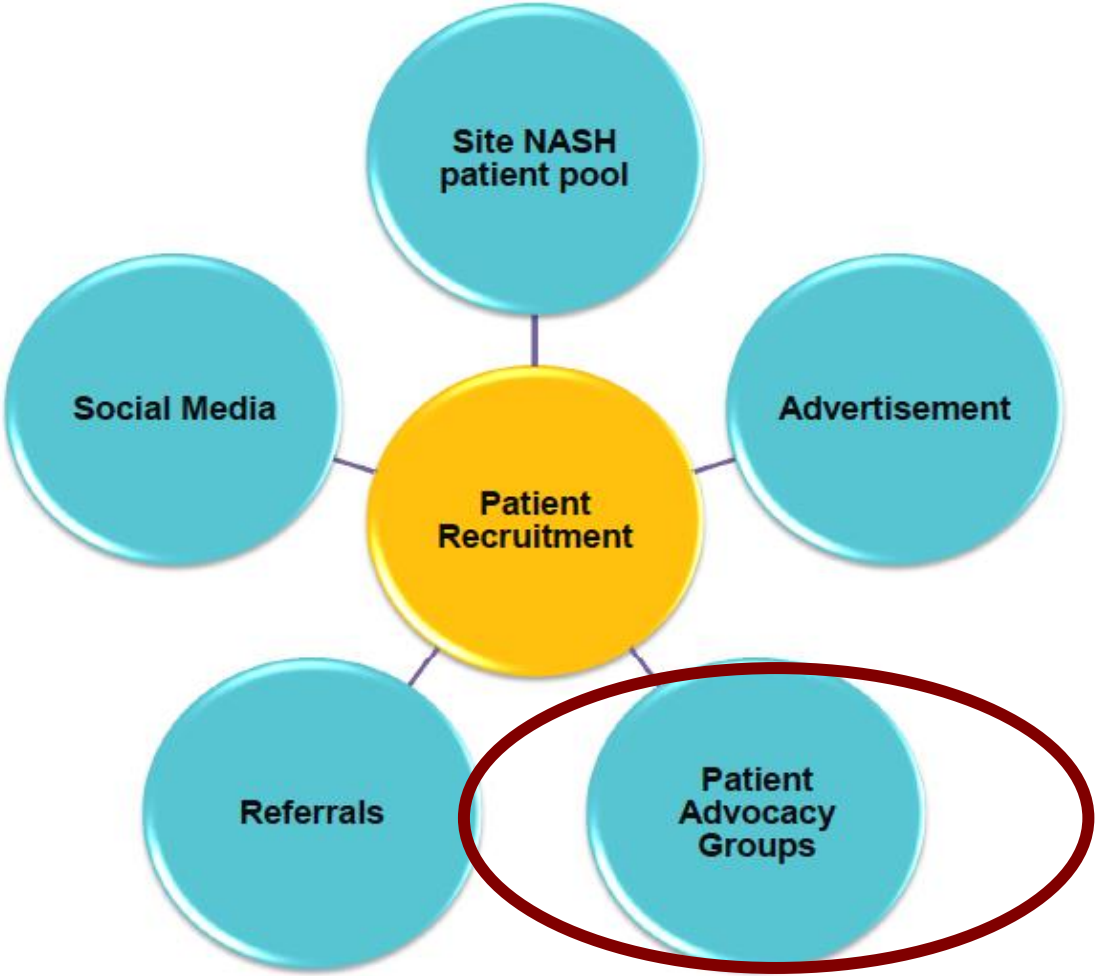
- Travel and meal reimbursement
- Parking ticket!

- Reminder messages
- “Thank you” messages
- Positive appreciation

- Some tools need EC approval (country-specific)

- No single tool will do the trick!!

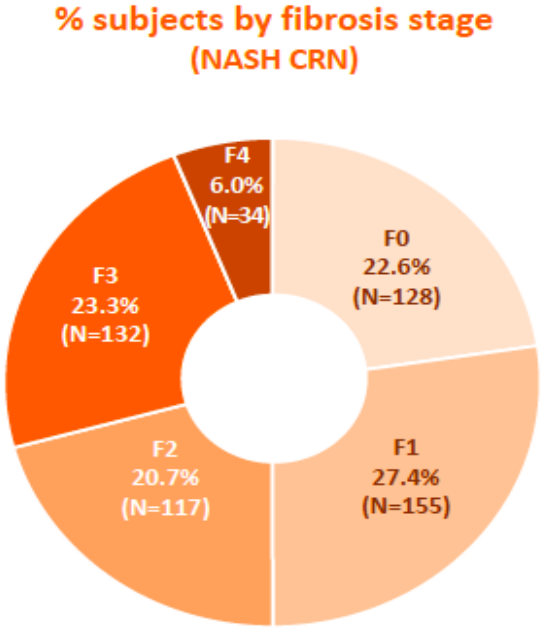

Education
Awareness
Appreciation
Relationships
Responsiveness
Resources
Communication


Site NASH patient pool
Social Media
Advertisement
Patient Recruitment
Referrals
Patient Advocacy Groups

Screening failure

- In- and exclusion criteria
  - ALT?
  - Requirements for glycemic control
- Concommitant medication
  - Especially for current phase 3 long term
- Stable condition before screening and study entry
  - Weight and physical activity
  - Anti-diabetic drugs and requirements for glycemic control
  - Lipid-lowering drugs
  - 6 month trial life style modification before trial entry
- Most frequent reason for SF is based on biopsy

Screening biopsies (N=566)



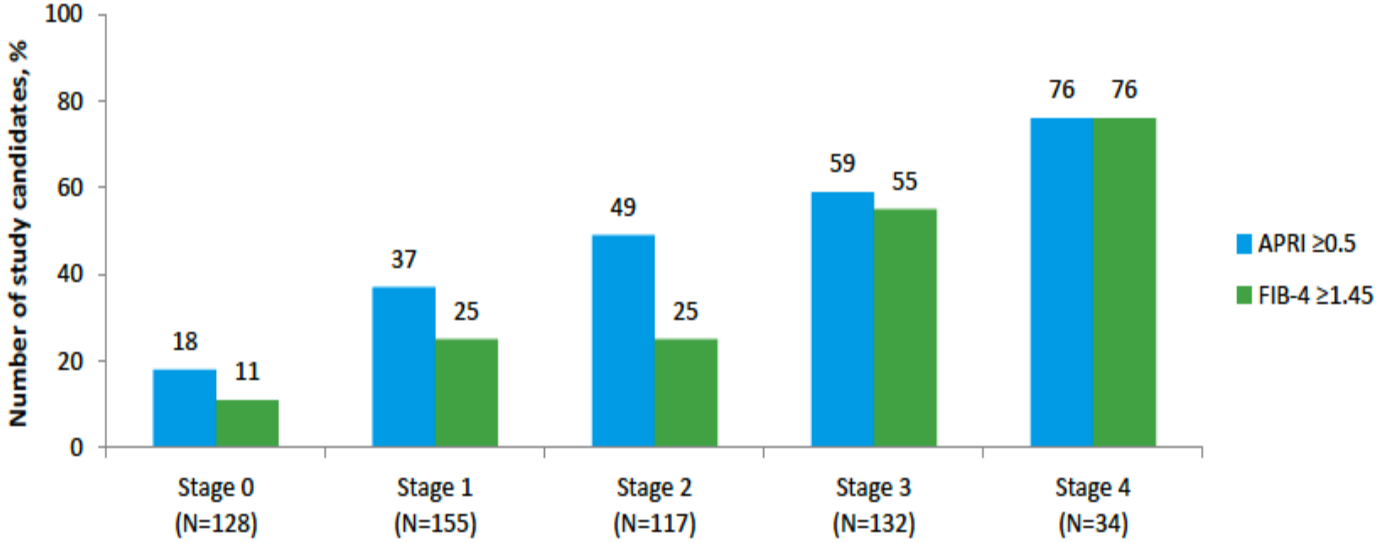
Almost a quarter of study candidates undergoing liver biopsy had no fibrosis at screening

812 -> 566 -> 289

Sanyal *et al*, DDW 2016 (Courtesy L. Fischer)
Goodman *et al*, ETC 2017 (Courtesy L. Fischer)

- Variable but sometimes quite high
- How to avoid?
  - “historical biopsy”
    - Local reading
  - Pre-screening
    - clinical characteristics, scores (NFS, FIB4,…), elastometry,…
      - Enrich population for more severe NASH + fibrosis
      - we need to work on algorithms
    - Biopsy upfront (so not within the screening period) and then further screening based on local reading of biopsy

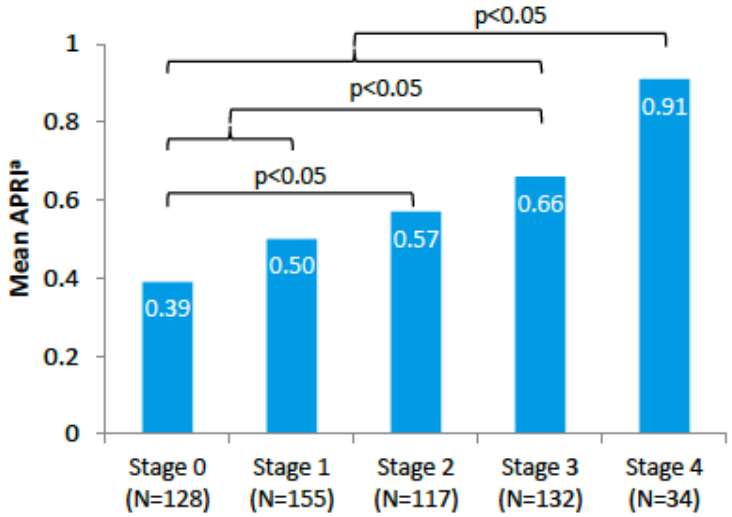
- Variable but sometimes quite high
- How to avoid?
- Central reading issues
  - Concordance or discordance with local reading
    - 1 or 2 expert pathologists (work load?)
  - Spare slides/material
    - Locally stained slides?
  - Long biopsy cut in 2 pieces



The proportion of screened candidates with elevated APRI (≥0.5) or FIB-4 (≥1.45) scores increased with fibrosis stage

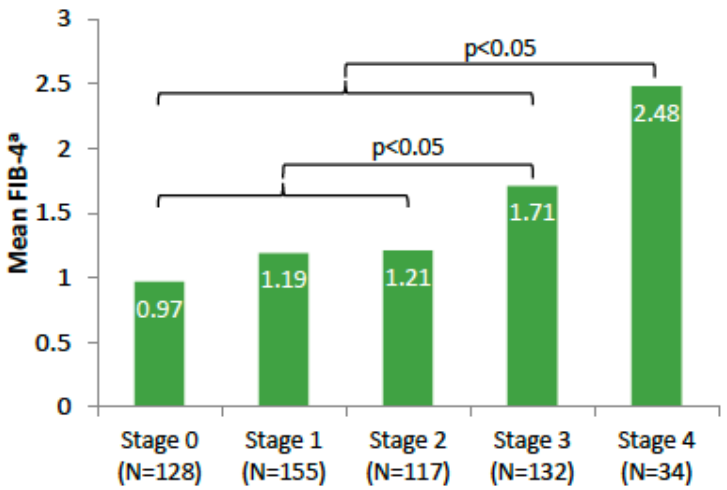
Sanyal *et al*, DDW 2016 (Courtesy L. Fischer)

Mean APRI and FIB-4 Scores By Fibrosis Stage



Significant differences in mean APRI scores were observed:

- between Stage 4 and all others (p<0.05)
- between Stage 3 and Stages 0 and 1 (p<0.05)
- between Stage 2 and Stage 0 (p<0.05)



Significant differences in mean FIB-4 scores were observed:

- between Stage 4 and all others (p<0.05)
- between Stage 3 and all others (p<0.05)